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**Via Electronic Filing**

Wayne E. Cascio, MD, FACC
Director, Center for Public Health and Environmental Assessment (CPHEA)
Office of Research and Development (ORD)
Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460

**Submitted via Regulations.gov**

**RE:** **Comments by Robert Golden (Owner, ToxLogic, LLC) and Stewart Holm (Chief Scientist, AF&PA & AWC) on the IRIS Draft Assessment of Asthma and Sensory Irritation Risk of Formaldehyde**

Dear Dr. Cascio:

Thank you for the opportunity to submit comments to the Environmental Protection Agency (the "Agency") on the IRIS Draft Toxicological Review of Formaldehyde – Inhalation (the "Review"). We wanted to address the Agency to the fact that two of our Formaldehyde (FA) manuscripts were not cited in the Review (Golden 2011, Golden and Holm 2017). It is important to note that these manuscripts report on critical aspects in the FA literature that have not been addressed in the Review. Including this information would supply useful perspective on the complex literature regarding the relationship between FA and asthma and sensory irritation and lead the Agency to different conclusions. EPA also does not include or discuss other publications that deserve more careful consideration. Our examination of the Review shows the following:

- EPA relies on two papers to derive a Point of Departure (POD) for asthma that show no positive association with the disease
- EPA failed to review and incorporate critical and relevant literature
- EPA failed to discuss studies accurately and transparently
- These failures have led to the lack of a proper Weight of the Evidence integration using the Best Available Science



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- EPA is overly conservative in its use of uncertainty factors leading to "acceptable concentrations" that are far below other recent regulatory evaluations of FA that use a practical Weight of the Evidence approach
- This conservatism has led to EPA-derived "acceptable" concentrations that exist in virtually no locations on the earth

EPA must correct the Review prior to it being used in any meaningful fashion such as for TSCA risk evaluation purposes.

***Asthma***

***EPA Must Use and Integrate Important Reviews of the Literature***

In the Review, EPA provides a summary of some of the primary literature and draws their own conclusions regarding what they perceive to be the pertinent scientific studies. While there are some chemicals where the number of useful studies is scant this is not the case with FA. For the endpoint of asthma there is an authoritative review (NAS 2000) and a comprehensive update (Kanchongkittiphon et al. 2015) involving 69 additional studies focused on indoor environmental exposures and exacerbation of asthma. According to Kanchongkittiphon, the review searches yielded 2,570 articles. After application of inclusion and exclusion criteria to the abstracts, they identified 162 articles of preliminary interest. They further excluded 99 studies after reviewing the full articles. Six additional peer-reviewed articles from reference lists or researchers' files were included. Finally, 69 articles were selected for the peer-reviewed assessment. They considered recent findings in conjunction with evidence cited in the IOM (2000).

Having ignored these two relevant and knowledgeable publications, EPA has ignored evidence on the key substances that are considered causally related to asthma. In doing so, the Review presents conclusions that are at complete odds with NAS and Kanchongkittiphon, both of which demonstrated a practical Weight of the Evidence approach.

As this review and follow-up confirmed, studies of asthma can be divided into those dealing with factors leading to the development of asthma and those dealing with factors that exacerbate the illness in the known asthma group. Most of the research on this topic address "asthma exacerbation," the onset or worsening of symptoms—some combination of shortness of breath, cough, wheezing, and chest tightness—in someone who already has developed asthma. In assessing potential exposures that might exacerbate asthma in children, NAS (2007), stated there was (1) sufficient evidence to conclude that there is a causal relationship between exposure to the allergens produced by cats, cockroaches, and house-dust mites and exacerbations of asthma in sensitized individuals; and environmental tobacco smoke (ETS) exposure and exacerbations of asthma in preschool-aged children and (2) sufficient evidence of an association between dog allergen exposure and fungal exposure with exacerbation of asthma in individuals specifically sensitized to these allergens. In addition, damp conditions or indicators of dampness (e.g., dust mite and fungal

allergens) are associated with the presence of symptoms considered to reflect asthma; (3) for nonacute, nonoccupational FA exposure, there was limited or suggestive evidence for an association with wheezing and other respiratory symptoms as well as inadequate or insufficient evidence to determine whether an association exists between FA exposure and asthma development; and (4) inadequate or insufficient evidence to determine an association between indoor residential VOC exposures and the development or the exacerbation of asthma.

Importantly, EPA provides a review of a subset of the relevant literature instead of a full Weight of the Evidence evaluation on asthma and allergy, when compared to the two reviews mentioned above and reaches a very different conclusion on the role of FA and asthma. EPA concludes that the "evidence indicates" a role of FA with "allergic conditions and current asthma symptoms or degree of asthma control" while the National Academy of Sciences and Kanchongkittiphon et al. (2015) find only limited or suggestive evidence of an association between FA exposure and exacerbations of asthma. The NAS definition for this category is as follows:

> **Limited or Suggestive Evidence for Association**
> *There is limited or suggestive evidence of an association between FA exposure and exacerbations of asthma, particularly through enhanced response to other allergens.*

Due to its incomplete review of the literature, this Review does not raise to the level of "Weight of the Evidence" using the "Best Available Science" as required by the Lautenberg amendments to the Toxic Substances Control Act (TSCA) (2016). As TSCA will rely on the Review to inform the Risk Evaluation we feel it should be required that EPA conduct a suitable review at this stage in the TSCA Risk Evaluation process. We also urge EPA to revise the document to reflect appropriately the conclusions of the current literature. Of note, the evidence provided in a recent paper (Golden and Holm 2017) that was not cited or integrated into the Review supplies a roadmap of why unrecognized exposure to acrolein is an important confounding factor in many indoor air-related studies focused on FA.

### *EPA Must Revise the Review to Include a Practical Weight of Evidence Evaluation on Asthma Using the Best Available Science*

It is well documented (i.e., Garrett et al., 1998, 1999; Rumchev et al., 2002, 2004) that other substances in indoor air (e.g., VOCs and fungal spores) can cause and/ or exacerbate respiratory symptoms quite apart from FA. Consequently, it is likely inappropriate to conclude that the results reported by Krzyzanowski et al. (1990) can be unequivocally attributed to FA alone in indoor air. EPA has used this study published 32 years ago as "eligible for POD derivation for current asthma prevalence." Findings of this study (i.e., Peak Expiratory Flow Rate or PEFRs) are questionable in view of the low levels of FA found in the homes and at odds with controlled human studies where FA was the only variable (e.g., Lang et al., 2009). In addition, as in most studies of this kind, the lack of

measurements of allergens or other chemical agents that may have been present in indoor air and possibly contributed to reported symptoms is a major confounder. Although the authors did report greater changes in PEFR in children than in adults, the use of this measure does not confirm the presence or absence of asthma or bronchitis or that FA (or something else) was responsible for this finding. This is the only study suggesting differential effects in children versus adults, hardly a convincing basis for concluding that children are more sensitive to FA.

EPA also states in Krzyzanowski et al. (1990), (a study used by EPA to develop a POD for "current asthma prevalence") that an "increased prevalence of current asthma was seen in the highest exposure group in a categorical analysis." It is unclear what data EPA are relying on in making this statement. However, as noted in Table 4 of this paper there are three exposure ranges reported, <40 ppb; 41-60 ppb; >60 ppb. There is no dose response exhibited in the data presented and the prevalence rate for asthma in the highest concentration group for children exposed to FA but not to environmental tobacco smoke **was 0**. The authors report, "...the prevalence rates of current asthma diagnosed by a doctor were significantly increased in children living in houses with high FA levels in the kitchen, **but only in those also exposed to ETS**." (Emphasis added). ETS is considered in the Kanchongkittiphon et al., 2015, review to be causally related to exacerbations of asthma in children. This incomplete presentation of the available data even in the studies EPA relies on is inherent in the Review and shows EPA's bias in the presentation of data.

***EPA Must Account for the Contributing Role of Acrolein***

The above noted substances potentially present in indoor air that can exacerbate childhood asthma, many with different levels of certainty, present a substantial challenge with respect to designing and interpreting studies. The discovery that acrolein, an aldehyde that is 200 times more potent as a sensory irritant than FA (Fowles and Dybing 2003) and ubiquitous in indoor air, was significantly associated with asthma, whereas FA was not (Annesi-Maesano et al. 2012). Since it is plausible that FA has served as an unrecognized proxy for acrolein in studies conducted to date, our review (Golden & Holm, 2017) summarizes the well-established dose–response aspects of FA-induced irritation and its potential to exacerbate asthma symptoms. This is followed by a discussion of the available data on acrolein in sufficient detail to document its likely role in exacerbating asthma due to its irritant properties. The implications of acrolein as a previously unrecognized confounder are that indoor air studies, which report associations between FA and childhood asthma, should be interpreted with caution unless/until potential contributions and/or associations with acrolein are also considered.

Even Annesi-Maesano et al, 2012, who EPA uses their data to provide a POD for "current asthma prevalence" stated, "Although small, the significant correlations between EIA and $PM_{2.5}$ and

acrolein represent an important message for public health as between 40% and 90% of people with asthma usually have EIA and could be at even higher risk when exposed to air pollution."

In addition, as noted by Leikauf (2002) due to ever-increasing acrolein emissions into the environment, acrolein as a direct irritant may increasingly become a health hazard in individuals with respiratory diseases such as asthma.

***Acrolein Sources in Indoor Air are Similar to FA***

Acrolein sources are similar to what has been observed for FA. For example, indoor cooking with various oils at temperatures of 180°C generates substantial amounts of acrolein (i.e., 5-250 mg/kg oil) after released into indoor air. Also, as reported in Ho et al. (2006), total emissions of acrolein from commercial kitchens in Hong Kong were estimated at 7.7 tons/year, far exceeding the annual vehicle emissions of acrolein in that city (1.8 tons/year).

In California (CARB 2001) statewide average ambient concentrations of acrolein in 2004, 2005, and 2006 were 1.21, 1.37, and 1.35 μg/m$^3$, respectively, based on routine air monitoring. Others (Gilbert et al. 2005) have also reported somewhat higher indoor air concentrations of acrolein from 0.1 to 4.9 μg/m$^3$. As summarized by Agency for Toxic Substances and Disease Registry (2007) the average environmental concentrations of acrolein in outdoor air range from 0.5 to 3.19 ppb and in indoor air range from <0.02 to 12 ppb in residential homes. In an analysis of indoor/outdoor acrolein air concentrations in 15 homes in Los Angeles County, outdoor acrolein ranged from 0.09 to 1.7 μg/m$^3$, whereas indoor air concentrations were approximately 10 times higher (i.e., 2.1-12.2 μg/m$^3$) (Seaman et al. 2007). The primary emission sources were due to multiple factors including heated animal or vegetable oils that produce noticeable spikes in indoor air acrolein concentrations, which increase with cooking. It was noted (Seaman et al. 2007) that the major finding of this study was that indoor concentrations of acrolein, one of the top hazardous air pollutants named by the USEPA and a known pulmonary toxicant, were 3 to 40 times higher than outdoor concentrations. In another similar study (Seaman et al. 2009), acrolein emission rates were measured from various cooking oils (canola, soybean, corn, and olive) used for deep-frying foods. Although the food items themselves made little contribution to air concentrations, cooking events involving the same food items resulted in acrolein air concentrations ranging from 26.4 to 64.5 μg/m$^3$.

In addition to cooking, environmental tobacco smoke (ETS) is a major source of acrolein in indoor air. To assess its contribution to exposure, two acrolein metabolites in urine, *N*-acetyl-*S*-(3-hydroxypropyl)-L-cysteine (3HPMA) and *N*-acetyl-*S*-(2-carboxyethyl)-L-cysteine (CEMA), were evaluated as biomarkers of acrolein exposure for the US population (Udeni Alwis et al. 2015). This analysis, based on data from the National Health and Nutrition Examination Survey (2005-2006) that accounted for age, sex, race, and smoking status, was designed to assess tobacco smoke as a predictor of acrolein exposure. Urine concentrations were dramatically higher in tobacco users

(cigarettes, cigars, pipes) compared to nonsmokers with median 3HPMA levels in smokers and nonsmokers of 1089 and 219 µg/g creatinine, respectively. Median CEMA urine levels of 203 and 78.8 µg/g creatinine were found for smokers and nonsmokers, respectively. These data demonstrate the substantial differences between smokers and nonsmokers with respect to acrolein exposure. In addition, when considering asthma, the importance of knowing the smoking status and ambient acrolein concentrations in studies attempting to discern relationships between indoor air factors and asthma exacerbations should be evaluated.

Therefore, it is reasonable to conclude that there is a sound exposure-based rationale for better understanding the potential health impacts of acrolein, particularly as they might relate to sensory irritation and asthma. EPA must incorporate this rational information into their Review.

***EPA's Review of the Literature is Incomplete***

A possible resolution of why so many studies have failed to demonstrate more than limited or suggestive evidence of an association between FA exposure and exacerbations of asthma is that unaddressed exposure factors in indoor air are confounding the reported findings. This is especially the case at the low FA air concentrations (i.e., <80 ppb) in most studies conducted in homes. A plausible explanation for this exposure–response dilemma may be found in a relevant study (Annesi-Maesano et al. 2012) that evaluated relationships between indoor air quality and asthma in 401 randomly selected classrooms from 108 primary schools attended by 6590 children (mean age 10.4 years). Air concentrations of $PM_{2.5}$, $NO_2$, and three aldehydes (acrolein, FA, and acetaldehyde) were measured, and health status variables, including skin prick testing to 10 common allergens, and exercise-induced asthma (EIA) were assessed for each participant. Potential confounders considered included age, gender, passive smoking, paternal/maternal history of asthma or allergic disease, dampness, gas appliance, ethnicity, and socioeconomic status. An increased prevalence of asthma in the past year was reported in children using classrooms with elevated levels of $PM_{2.5}$, $NO_2$, and acrolein. Rhinoconjunctivitis was the most common condition observed followed by EIA and asthma, with allergic asthma more frequent than nonallergic asthma.

EPA stated that Annesi-Maesano et al. (2012), reported that FA was significantly associated with rhinoconjuctivitis at median reported FA levels of 21 ppb. However, these levels at which rhinoconjunctivitis (i.e., eye/nose irritation) occurred appear inconsistent with substantial data on dose–response aspects of FA-induced sensory irritation from controlled human studies reported by others. This endpoint is likely confounded by other causally associated substances in indoor air that were not measured in this study and not considered by EPA. This endpoint should not be considered causally related with FA and the study should not be used to derive a POD.

Importantly, Annesi-Maesano et al. (2012) reported that FA was not associated with asthma in this study. Acrolein was the only exposure significantly associated with both asthma (OR: 1.37,

95% CI: 1.14-1.66) and allergic asthma (OR: 1.41, 95% CI: 1.16-1.73) whereas $NO_2$ was statistically significantly associated with asthma (OR: 1.18, 95% CI: 1.01-1.39). FA was statistically significantly associated only with rhinoconjunctivitis (OR: 1.41, 95% CI: 1.08-1.85) but not with asthma. When the total population was stratified based on a positive skin prick test to ten common allergens, which is a measure of atopy, $PM_{2.5}$, acrolein, and $NO_2$ were significantly related to allergic asthma. The only significant positive correlation in this study was between EIA and levels of $PM_{2.5}$ and acrolein in the same week.

These are the only data that have (1) separately documented irritant, but not asthma, symptoms from FA and (2) accounted for the potential contribution of acrolein, a potent upper and lower respiratory tract irritant. Importantly, acrolein is mechanistically and etiologically associated with asthma but has never previously been considered in any of the numerous indoor air studies investigating potential associations between FA and asthma.

EPA also relies on Annesi-Maesano et al. (2012) to derive a POD for asthma. In the Review (p. 1-99) it states a 6.9% prevalence of asthma resulting from FA exposure. Additionally, the Review states that the study indicates an "absence of risk of current asthma below 0.05 mg/m$^3$." The 6.9% prevalence rate is located in Table 2 of the paper. However, this result is for the studied cohort and does not discuss an association with FA anywhere in the table or the text of the paper. Also in the Review, Figure 1-11 is incorrect. This figure shows increased relative risks for both atopic (allergic) asthma and non-atopic (non-allergic) asthma in the highest category of FA exposure. There are no data in the paper to support these relative risks reported by EPA.

Comparing the actual data in the paper show that for the high dose of FA there is an increase in rhinoconjunctivitis (1.19) a **decrease** in asthma in the entire sample population (0.90), a **decrease** in asthma in atopic children (0.96) and a **significant decrease** in asthma among non-atopic children (0.82). Yet, EPA has used this study to incorrectly include a FA POD for current asthma prevalence. The use of this study to derive or support a Reference Concentration for FA is not consistent with the Best Available Science.

***Sensory Irritation***

- EPA's Reliance on Residential or Home studies is Misguided and is not the Best Available Science
- EPA Should Rely on Human Volunteer Chamber Studies that have Proper Controls to Reduce or Eliminate Confounding Factors and False Positives
- EPA Fails to Rely on Mueller et al., 2013, and Lang et al., 2008, that are considered by many countries as "critical studies" (e.g., France, Netherlands, 2019)
- EPA's representation of the Sensory Irritation Studies as an Adverse Health Effects cannot be considered the Best Available Science

**EPA Should Not Rely on Home Studies that have Known Confounders and Bias**

With respect to studies conducted in residential settings, a NAS (2007) committee expressed skepticism about the use of such studies rather than those conducted under controlled conditions. Indeed, the most recent Scientific Committee on Occupational Exposure Limits (SCOEL) 2016, recommendation states that, "the most reliable data are obtained in controlled studies with volunteers."

Most studies conducted in residential dwellings (including both conventional homes as well as manufactured housing such as trailers and mobile homes) with the goal of assessing potential FA-related effects on sensory irritation are also typically confounded by co-exposures to acrolein, active smoking, ETS, VOCs, smoke from wood fires, cooking fumes, house dust, pet dander, molds, fungi, etc. These co-exposures make it impossible to conclude with confidence that any results reported are due solely to FA. In addition, the results of some residential and/or community studies can also be confounded by selection bias (e.g., offers of free testing due to adverse publicity, emotional media stories, etc.), which can be substantially influenced by false-positive results (i.e., reporting of symptoms in the absence of FA or at concentrations insufficient to elicit symptoms [e.g., Main et al., 1983; Bracken et al., 1985; Kilburn et al., 1985; Imbus et al., 1985; Anderson et al., 1979; Ritchie and Lehnen, 1987]). A striking example of these issues is illustrated by a study that actually assessed whether effects attributed to FA in a residential setting might be confounded by other exposures and/or psychological factors. Broder et al. (1991) investigated a large group of about 200 control homes and 600 houses that had been insulated with urea FA foam insulation (UFFI) and then, due to complaints and government provided subsidies for UFFI removal, about half of the UFFI houses were remediated to remove the insulation. Each of the houses and occupants were investigated on two occasions separated by an interval of 12 months. In the first survey of the population, prior to remedial work, there was a moderate excess of many signs and symptoms of irritation, including nasal problems, eye, throat discomfort, cough, headache, and dizziness. These symptoms were associated with an exposure-response relationship between FA levels in the UFFI homes (0.046 ppm), but no such relationship in control homes (0.035 ppm). In the second survey conducted in controls and houses following UFFI removal, there was an appreciable reduction in the reported incidence of irritation symptoms and the disappearance of the exposure-response relationship, even though the remediation efforts had no effect on FA levels in the remediated homes (0.044 ppm). The authors concluded that the symptoms in the initial survey were not due to FA alone and that their observations were "...indicative of the complexities that may arise in assessing and understanding health risks...related to chemicals in indoor air."

***EPA Must Focus on Chamber Studies that have Proper Controls***

Early studies that investigated the irritant properties of FA generally did not properly account for its characteristic acrid or pungent odor. The ability of most individuals to detect the odor of FA is typically more sensitive than the lowest exposure level that produces the symptoms of sensory irritation. Therefore, studies designed to evaluate the irritation threshold must account for the odor of FA by masking it with an odoriferous but non-irritating substance, such as methyl mercaptan, in order to account for this confounder. Failure to do so raises the likelihood that subjects will confuse the odor with symptoms of sensory irritation (Lang et al., 2008). Without accounting for the confounding effects of odor, some early, largely uncontrolled, studies suggested that sensory irritation from FA was on the order of less than 0.01 ppm (10 ppb). Those studies did not control for the misinterpretation of odor detection as sensory irritation (Abraham, 2001) or for behavioral sensitization to the odor of FA (and other highly odoriferous compounds), which confounds the study of other properties of these compounds such as sensory irritation (Shusterman et al., 1988). Properly conducted studies, using appropriate controls, have more accurately determined the ability of humans to detect the odor of FA. These studies have failed to confirm the ability of even the most sensitive individual to detect exceedingly low concentrations of FA. For example, ATSDR (2008) lists the lower level of odor detection as 0.5 ppm. This level has been confirmed by a number of human volunteer chamber studies, which have placed significant emphasis on removing the odor bias associated with FA exposure (Iwasaki and Ishiguro, 1978; Leonardos et al., 1969; Hellman and Small, 1974). Like the majority of other odoriferous compounds, FA has an odor threshold that is typically less than its irritant threshold. This has been confirmed by a number of studies that have examined the ability of several groups to detect sensory irritation of FA (e.g., Arts et al., 2008).

***EPA's Must be Realistic in Calculating Reference Concentrations***

Controlled chamber studies expose human volunteers to known concentrations of FA, with the best of these studies including clean air controls (i.e., 0 ppm FA), in order to unequivocally determine the air concentrations of FA that can reliably elicit symptoms of sensory irritation in the absence of any potential confounders. Some of these studies have also masked the odor of FA in order to eliminate odor alone as the "cause" of symptoms of sensory irritation. In an extensive review, Paustenbach et al. (1997) convened a panel of experts who evaluated approximately 150 studies, 52 of which were human studies with ten of greatest relevance for establishing a concentration response relationship for sensory irritation. As discussed in this review, "The panel concluded that for most persons, eye irritation clearly due to FA does not occur until at least 1.0 ppm. Information from controlled studies involving volunteers indicated that moderate to severe eye, nose, and throat irritation does not occur for most persons until airborne concentrations exceed

2.0–3.0 ppm. Based on the **weight of evidence** from published studies, the panel found that persons exposed to 0.3 ppm for 4–6h in chamber studies generally reported eye irritation at a rate no different than that observed when persons were exposed to clean air." This conclusion is notable because all subsequent independent reviews, which incorporate additional controlled human studies performed since Paustenbach (1997), have reached essentially identical conclusions. The Organisation for Economic Co-operation and Development Screening Information Data Set (OECD/ SIDS, 2002) concluded, "Studies in the literature have reported a variety of responses induced by exposure to gaseous FA, generally beginning in the range of 0.3 to 0.5 ppm for eye irritation, the most sensitive endpoint. However, the severity of response at these levels is generally mild, and only a small portion of the population may respond." Moderate eye, nose, and throat irritation occurs at 2 to 3 ppm. The majority of critical assessments of FA levels that would be protective for the symptoms of sensory irritation for all individuals, including those with self-reported sensitivity to FA as well as asthmatics, support the lowest effective irritant concentration of 0.3 ppm.

Several important weight of the evidence reviews have used these data to calculate acceptable concentrations in the range of 0.1 ppm with uncertainty factors of between 3 and 6 applied. Obviously, these evaluations result in concentrations much higher than EPA's inappropriate use of the literature and failure to use an appropriate weight of evidence evaluation from published studies and in clear violation of the use of Best Available Science.

## Conclusions

### *Asthma*

As summarized in these comments, with respect to identifying potential risk factors in indoor air that might exacerbate asthma, the emphasis should be on exposures of most concern based on the level of empirical evidence for each factor. This is particularly relevant for childhood asthma, which has been growing in prevalence with indoor air, an important contributing factor. The only way to accomplish this in the most scientifically defensible and cost-effective manner is to focus research and communication efforts on those factors with the highest level of confidence that they are causally associated with asthma, either incident disease or exacerbations. This issue has been repeatedly addressed in comprehensive evaluations (NAS 2000, Kanchongkittiphon et al. 2015, SCOEL, 2016). These analyses rely on well-established weight of evidence evaluation factors to critically assess the available scientific data for various exposures of potential concern and the extent that each satisfies the weight of evidence categories: (1) causal, (2) sufficient, or (3) limited/suggestive.

This is particularly evident in more rigorously conducted studies that can reveal true causal associations between indoor air factors and exacerbations of childhood asthma. For example, an extensive investigation (Teach et al. 2015) of seasonal risk factors for asthma exacerbations was

conducted in 456 inner city children aged 12 to 20 years in ten large urban research centers in the United States. The most relevant statistically significant factors germane to this review were increases in positive allergen skin test results for rodents (OR: 2.05, 95% CI: 1.14-3.68), cockroach (OR: 1.93, 95% CI: 1.03-3.61), allergen-specific IgE levels to house-dust mite (OR: 1.46; 95% CI: 1.02-2.09) and cockroach (OR: 1.48, 95% CI: 1.06-2.06). Notably, all the above exposure factors are known to be causally associated with asthma. These results highlight the need to investigate and focus on factors known to be causally associated with asthma exacerbations, rather than FA for which the evidence does not rise to this level of confidence. The discovery that acrolein is virtually certain to have been present in the indoor air of all studies in which FA has been implicated as associated with asthma should raise a red flag with respect to their conclusions.

So, reported conclusions in the numerous studies that attribute respiratory and/or asthma effects uniquely to FA must be questioned. This is particularly evident at FA concentrations well below conservative guidelines (e.g., WHO, Norway, Australia, Japan, etc., [100 µg/m$^3$] and Canada [50 µg/m$^3$]) which underscore the likely contribution of acrolein. The implications of not considering acrolein in such studies are also suggested in a comprehensive review (Mendell 2007) of indoor residential chemical emissions as risk factors for respiratory and allergic effects in children. Twenty-one indoor air studies were the basis of this evaluation. As noted in this evaluation:

> Many of the risk factors investigated in these observational studies are highly correlated with each other and probably also with other true causes not studied. This source of confounding can produce spurious reported risk estimates for investigated compounds. Adjusting in statistical models simultaneously for the multiple risk factors investigated will at least reduce confounding bias among these risk factors, although confounding by other unmeasured risks can persist. Furthermore, perhaps the most important source of bias in this body of research, even in the well-designed studies, is confounding.

If FA is believed to be an important risk factor with respect to its potential contribution to asthma exacerbations in children, this conclusion cannot be supported until contributions from acrolein are considered. Other than a single study Annesi-Maesano et al. (2012), none of the other studies currently relied upon with respect to the FA/asthma issue in childhood considered co-exposures to acrolein. Consequently, conclusions with respect to FA alone can only be considered as suspect. This is particularly the case since acrolein is a demonstrably more potent respiratory tract irritant than FA, with the clear ability to exacerbate asthma symptoms. The only way that this dilemma can be resolved would be to conduct a chamber study with filtered air or to conduct additional epidemiological studies, in which air concentrations of both FA and acrolein are quantified in order to assess possible correlations between these irritants. Such information would provide information sufficient to apply to the "Weight of the Evidence" using the "Best Available Science" as required under the amended TSCA.

Since there are no meaningful physiological differences between children and adults with respect to irritant responses to FA in the upper respiratory tract, asthmatic children would appear to share with adult's similar insensitivity to FA exposure and asthma. Although asthma exacerbations from substances in indoor air are clearly a public health issue that needs to be addressed, the focus should be on those constituents for which the data are either causally or significantly associated with this disease. With the potency of acrolein far greater than FA as a respiratory irritant and now identified as either (1) a probable confounder of previous studies in which FA was a principal focus or (2) at least significantly (or much better causally) associated with asthma on its own, should serve to minimize the present emphasis on FA. For example, if a study on potential risk factors for childhood asthma is conducted in inner city dwellings it would be remiss to ignore the substantial known contribution from cockroach antigen as a contributor to asthma symptoms. Similarly, as summarized in this review, the same should now be obligatory for acrolein in all studies moving forward. Since EPA has concluded that acrolein is responsible for about 75% of noncancer respiratory health effects attributable to air toxics in the United States, and with indoor air levels up to ten times or greater than outdoors, there must be a reasonable effort to address this issue. Until and unless this is done, it is inappropriate to focus solely on FA as playing a meaningful role in asthma symptoms without accounting for acrolein confounding.

Finally, EPAs' misrepresentation of the two studies (Krzyzanowski et al., 1990; Annesi-Maesano et al., 2012) it relied on to derive a POD cannot be ignored. EPAs' bias against the chemical to even use a negative study in support of an association is a failure of the best available science.

***Sensory Irritation***

A crucial distinction between controlled studies and those where responses are simply reported based on ambient exposure levels (whatever they might be) is that it is difficult (if not impossible) to reliably determine whether FA actually causes irritation at levels below about 1 ppm. This is because when some people are intentionally exposed to air with FA levels below 1 ppm and some are exposed to clean air (i.e., FA-free), 20–30% of those exposed to clean air will still report responses of sensory irritation (i.e., false positives) (Bender, 1983; OECD/SIDS, 2002). For example, after reviewing this large body of data, the Australian government (NICNAS, 2006) determined that "…chamber studies also found that some individuals begin to sense irritation from 0.5 ppm (0.6 $mg/m^3$), although the response rate is often similar to that reported in controls. There is limited evidence that some individuals report sensory irritation as low as 0.25 ppm (0.3 $mg/m^3$), however, the data is very unreliable. Therefore, the lowest observed effect level (LOEL) is considered to be 0.5 ppm." Although there are no data specifically identifying different FA concentrations below 1 ppm and the associated frequencies of false-positive reports of sensory irritation, it appears reasonable that such reports would be greater at 0.1 ppm than at 0.3 ppm, the consensus level below which sensory irritation is unlikely to occur. This is why, for example, that the residential studies that report

unequivocal symptoms of sensory irritation at 0.1 ppm, but lack a clean air control (e.g., Ritchie and Lehnen, 1987; Main and Hogan, 1983), do not provide a credible basis for drawing conclusions concerning airborne concentrations of FA that might be associated with sensory irritation.

The conclusion that an exposure limit of 0.3 ppm FA in indoor air is conservative and health protective is fully supported by recent independent evaluations. For example, in an evaluation of the human data on FA a Dutch review noted that "...it can be concluded that minimal/mild/slight eye irritation starts at levels of 1.0 ppm FA and higher." The same review also concluded that nasal and throat irritation start at FA levels of 2.0 ppm and 3.0 ppm, respectively (TNO Nutrition and Food Research, 2003). Of interest to this review, in deriving Acute Exposure Guideline Levels (AEGLs), US EPA (2004) selected 0.9 ppm as the AEGL for an 8-hour exposure, noting that "At 0.35 to 0.9 ppm, the subjects subjective eye irritation responses ranged from none to slight, the same as their responses to clean air."

As for the POD, EPA has chosen to rely on studies published in the 1980s (Hanrahan et al, 1984, Kulle et al., 1987) instead of state-of-the-art studies that were published in this century (Mueller et al., 2013, Lang et al., 2008). EPA stated that the rationale for decision not to advance was "Difficult to define an adverse response level cutoff for these endpoints," which aligns with the difficulty in categorizing these low concentration sensory effects as adverse.

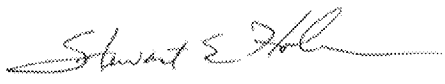
Other reviews that included Mueller et al. and Lang et al. did not have these perceived difficulties. For example, the European Commission Scientific Committee on Occupational Exposure Limits (SCOEL) noted that with the availability of two volunteer exposure studies complementing each other and not only measuring subjective reporting but also objective signs of eye and upper respiratory tract irritation (Lang et al., 2008; Mueller et al., 2013), an exposure limit can now be based on objective parameters not potentially biased by personality traits like anxiety or expectations.

The No Observed Effect Level (NOEL) was based on 62 volunteers (41 in the Mueller study and 21 in the Lang study) is sufficiently robust for the derivation of a Limit Value. No further uncertainty factor for possible human inter-individual variations is necessary, especially as low interindividual variation is also confirmed by the older studies reviewed by Paustenbach et al. (1997), and these effects are not "adverse" effects which effect the form or function of an organism, as defined by EPA. Also, it has been suggested that an interspecies extrapolation factor of three for extrapolating animal data to humans concerning local irritation effects, but this may be reduced to two because of existing modellings of the airway physiology and FA deposition of rats and humans. Starting from the NOAEC of 1 ppm for tissue irritation in rats this would lead to 0.5 or 0.3 ppm similar to the NOECs for sensory irritation found in human volunteers. This example of appropriate data integration has not been seen and should be considered in the Review.

The current Review demonstrates misunderstandings of this complex data set and truncated descriptions of the scientific studies on asthma and sensory irritation. The Review appears to be

searching for the lowest possible concentrations by whatever means possible instead of providing a weight of the evidence approach using the Best Available Science. The document must be rewritten objectively and thoroughly to provide any program office including TSCA the best information to conduct an appropriate Risk Evaluation.

Best Regards,



Stewart Holm
Chief Scientist
American Forest & Paper Association

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